# POSSIBILITY OF INDUCTION OF COMA WITHOUT ACCOMPANING CONVULSION BY ELECTRICAL AND CHEMICAL STIMULATION IN THE CENTRAL GRAY MATTER OF THE MIDBRAIN

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by

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## INTRODUCTION

Previously, TAKETOMO and TODA in our laboratory, demonstrated that when faradic stimulation was applied in the central gray matter of the midbrain from the level of the oculomotor to that of the trochlear nuclei in rabbits and cats, temporary coma could occasionally be induced. But, in many cases of faradic stimulation, elicited coma was accompanied with generalized convulsion, so that we could not distinguish whether the disturbance of consciousness was primary or secondary to convulsion.

In head injuries of man, especially commotio cerebri, coma occurs only temporarily and is scarecely accompanied with convulsion. Thus, I have attempted in animals (cats) to determine the adequate stimulation conditions and methods of easily inducing coma without accompaning convulsion by electrical and chemical stimulation in the central gray matter of the midbrain.

## EXPERIMENTAL METHOD

Unanesthetized adult cats were used for experiments. A cat was fixed on a hammock in prone position and her four limbs were allowed to hang down naturally through the holes of the hammock. Thus, it was possible to observe the behavior of the cat (movement of four limbs, convulsion, muscle tonus etc.) easily.

Under ether anesthesia the cat was fitted up with the HORSLEY-CLARKE's stereotaxic instrument (hang down type) on the head and a trephine opening (ca. 1 cm in diameter) was made in the parietal region. Then, after the animal had completely been awakened from anesthesia, I performed punctures of the brain stem under the guide of the instrument, using the electrode or the injection needle.

(1) Electrical stimulation

The electrode consists of iron wire 0.3 mm in diameter covered with insulating enamel, except for 0.3 mm at the tip, and was used for either monopolar or bipolar stimulation (pole distance: ca. 0.1 mm or ca. 2 mm).

Square pulse stimulation was done, and after this experiment, important

stimulated points were marked by electrocoagulation.

(2) Chemical stimulation

For chemical stimulation, a needle of ca. 1/4 mm in outer diameter and 13 cm in length was used, and attached to a luetin syringe (0.01 cc per one scale).

Strychnine, acetylcholine, penicillin, INAH (isonicotinic acid hydrazide), TEAB (tetra-ethyl-ammonium-bromide) were used as chemical stimulants to which a small amount of India ink was added to mark the location of stimulated points.

Histological examination

After the experiment, the cat was sacrificed by cutting both carotid arteries, and its brain was fixed in alcohol absolutus, embedded in celloidin, sectioned serially and the stimulated portion was confirmed by histological examination with following three staining methods.

a) Nissl's stain for nerve cells.

b) Yashiro's stain for myelin sheath.

c) Iron-carmine stain for settled ionic iron in points of electrical stimulation.

The criteria for judging the disturbance of consciousness in cats are as follows:

1) Unresponsiveness Ⅰ (semicoma Ⅰ)

Postural reflex is somewhat feeble. Searching reaction to light and sound, and flight reaction induced by touch or pressure to the body surface are almost absent. But the animal still reacts to painful and smell stimuli very strongly (Girndt Ⅱ-Ⅳ).

2) Unresponsiveness Ⅱ (semicoma Ⅱ)

Postural reflex is completely abolished. Active movements and reflexes to smell stimuli are abolished too. The reflexes to visual, acoustic and touch sense are also absent. The reflexes to painful stimuli against the body surface are almost abolished, but partially remain. The sneeze reflex by stimulating nasal septum, the reflex to painful stimuli of nasal apex and vomiting reflex due to stimuli of pharyngeal mucosa remain (Girndt Ⅳ-Ⅴ).

3) Unresponsiveness Ⅲ (coma)

The reflex due to stimuli of nasal apex and nasal septum and vomiting reflex due to stimuli of pharyngeal mucosa are absent. But corneal reflex, pupilary reflex and pinna reflex are sometimes present. Patellar reflex remains (over Girndt Ⅴ).

Among these criteria the postural reflex was difficult to observe during the experiment on account of fixation of the head. I mainly decided the disturbance of consciousness by the presence or absence of noci-reflexes.

## EXPERIMENTAL RESULTS

A) Stimulation by square pulses

1) Conditions of stimulation

Pulse duration was most commonly 1 msec, but sometimes 0.2 or 3. However, there were no remarkable differences in the effects of stimulation between 1 msec and others.

Cycle and voltage were variously changed in each case to investigate the

resulting reactions. But intensity of stimulation was under the threshold of convulsion, and did not change during stimulation in all cases.

2) Changes of behavior of experimental animal (cat)

The behaviors of cats were classified into three groups. i. e.,

(1) Disturbance of consciousness Type : { Coma / Semicoma Ⅱ / Semicoma Ⅰ

(2) Agitation states Type : { Sham rage / Excitation

(3) Showing no behavioral change.

a) Stimulation with monopolar electrode

Cases Nos. 4, 6, 7, 11.

The electrode was exactly inserted in 6 points in the central gray matter of the midbrain histologically (In the following, the central gray matter will be abbreviated as GC.).

In 2 out of 6 points, "semicoma Ⅰ" and "semicoma Ⅱ" were elicited. But in the remaining 4, in spite of the fact that the sites of stimulation were found in the GC, the cats showed "agitation states" or "no behavioral change".

All cases in which the outside the GC was punctured indicated the "agitation states", and did not indicate any disturbance of consciousness.

With monopolar electrode, coma did not result from the stimulation of any points of mesencephalon.

The relation between the sites of stimulation and the behaviors is shown in Table 1.

**Table 1**

| Sites of Stimulation / Behaviors of Cats | GC | Outside GC |
|---|---|---|
| Coma | 0 | 0 |
| Semicoma Ⅱ | 1 | 0 |
| Semicoma Ⅰ | 1 | 0 |
| Sham rage | 3 | 1 |
| No behavioral change | 1 | 0 |

Conditions of stimulation and behaviors of cats are shown in Table 2.

**Table 2**

| Behaviors of Cats | Duration | Voltage | Cycle |
|---|---|---|---|
| Semicoma Ⅱ | 1 msec | 2 volts | 60 cps |
| Semicoma Ⅰ | 1 msec | 1.5 volts | 100 cps |
| Sham rage or Excitation | 1 msec | 1.5 volts | 60 cps |

b) Stimulation with bipolar electrode

1) Pole distance ca. 0.1 mm

6 cases (Nos. 5, 15, 20, 35, 57, 58). In 4 cases (Nos. 20, 35, 57, 58) the stimulated points were recognized in the GC, and in the remaining 2 (Nos. 5, 15) they were found in the superior colliculus.

Out of these 6 cases, 1 (No. 35) fell into coma and the other 1 (No. 20) fell into semicoma, and the remaining 4 indicated "sham rage" or "no behavioral change".

The relation between sites of stimulation and behaviors of cats is shown in Table 3.

Experimental protocol of 1 case (No. 35) which fell into coma was as follows.

Cat (No. 35), 2.4 kg, female.

Under the control of the HORSLEY-CLARKE's stereotaxic instrument, electrical stimulation with bipolar electrode was given through the trephine opening to the midbrain, when the cat had completely recovered from ether anesthesia and noci-reflexes were normally present.

**Table 3**

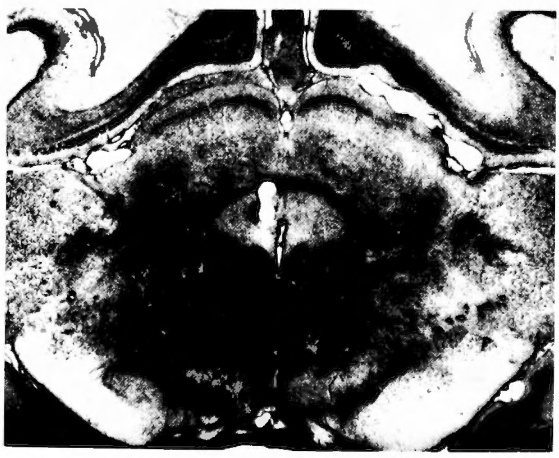
| Sites of Stimulation / Behaviors of Cats | GC | Outside GC (superior colliculus) |
|---|---|---|
| Coma | 1 | 0 |
| Semicoma Ⅱ | 1 | 0 |
| Sham rage | 2 | 0 |
| No behavioral change | 0 | 2 |

Mere puncturing with an electrode made no animal unconscious.

As soon as the current was transmitted under the conditions of 1 msec, 1.5 volts, 60 cps, the cat abruptly stopped movement, the pupils were somewhat dilated, but anisocoria did not exist. Pharyngeal reflex was abolished. Mandibula was almost flaccid. Ear lobe responded to painful, touch or heat stimuli, but the avoiding reaction was weaker than before the electrical stimulation. The cat did not cry and the respiration was almost normal. Active movements were not observed in four limbs. Namely the cat was induced in the state of "semicoma Ⅱ". When conditions of stimulation were intensified up to 1 msec, 2 volts, 60 cps, the pupils were fully dilated, the corneal reflex, pharyngeal reflex were abolished, and pinna reflex was almost absent, and then the cat fell into coma with loss of all noci-reflexes. With coma whole body became flaccid, and the cat continued the state of coma for about 1 minute without accompaning convulsion. Afterwards, although the stimulation was continued, noci-reflexes were gradually recovered and the cat turned into the state of semicoma. When the current was stopped, the cat abruptly arose from the state of coma or semicoma.

Next, when both cycle and voltage were changed, the pulse duration being constant at 1 msec, the cat similarly fell into coma. The relation between cycle and

**Fig. 1**



No, 35
Transverse section of the midbrain showing the site of stimulation.

voltage was as follows:

30 cps ..... ca. 3 volts,
100 cps ..... ca. 2 volts,
180 cps ..... ca. 1.7 volts.

Namely, for causing coma it seemed likely that when cycle was increased, the voltage could be lowered.

Histologically, the tip of electrode was recognized in the dorsal portion of the GC as shown in Fig. 1.

In one case of "semicoma Ⅱ", noci-reflexes were almost abolished, but pinna reflex remained slightly. Stimulation conditions in this case were almost the same as in the coma case (1 msec, 2 volts, 60 cps). The semicoma animal showed somewhat increase of muscle tonus, and stretch position, although the active movements of four limbs were absent.

Histologically, the stimulated point was recognized in the ventral portion of the GC near the oculomotor nuclei.

Other 2 cases which were stimulated in the GC showed "sham rage" reaction. The cats violently cried and writhed. The muscle tonus of whole body was enhanced. And in the remaining 2 cases, which were stimulated outside the GC (near the superior colliculus), distinct changes in behavior were not recognized.

2) Pole distance ca. 2.0 mm

To observe the behaviors of cats, when the GC was stimulated in a wider extent, I performed the stimulation by a pair of monopolar electrodes inserted ca. 2 mm apart in parallel in sagittal plane.

Experimental animals 14. Stimulated points 17. In all these cases the locations of 2 tips of the front and rear pole were exactly demonstrated histologically.

Relation between the sites of stimulation and the behaviors of cats is indicated in Table 4.

**Table 4**

| Sites of Stimulation / Behaviors of Cats | GC | Outside GC |
|---|---|---|
| Coma | 4 | 0 |
| Semicoma Ⅱ | 2 | 0 |
| Semicoma Ⅰ | 1 | 0 |
| Sham rage | 8 | 0 |
| Excitation | 1 | 0 |
| No behavioral change | 0 | 1 |

There were 4 cases (Nos. 11, 12, 19, 66) which fell into coma.

(a) The sites of stimulation in these cases

3 of 4 cases were stimulated in dorsal part of the GC and the remaining 1 case was stimulated in ventral part as shown in histological specimen (Fig. 2).

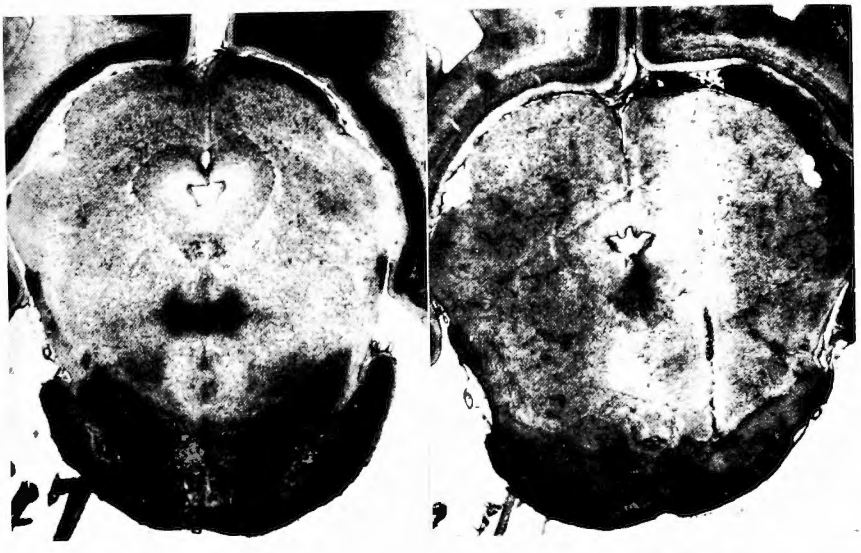
(b) Conditions of stimulation

As shown in Table 5, 1 msec, ca. 1.5 volts, ca. 60 cps were employed in cases Nos. 11, 12, 19. In case No. 66 in which the electrode tip was about 2 times larger, cycle and voltage were lower than in the other 3 cases.

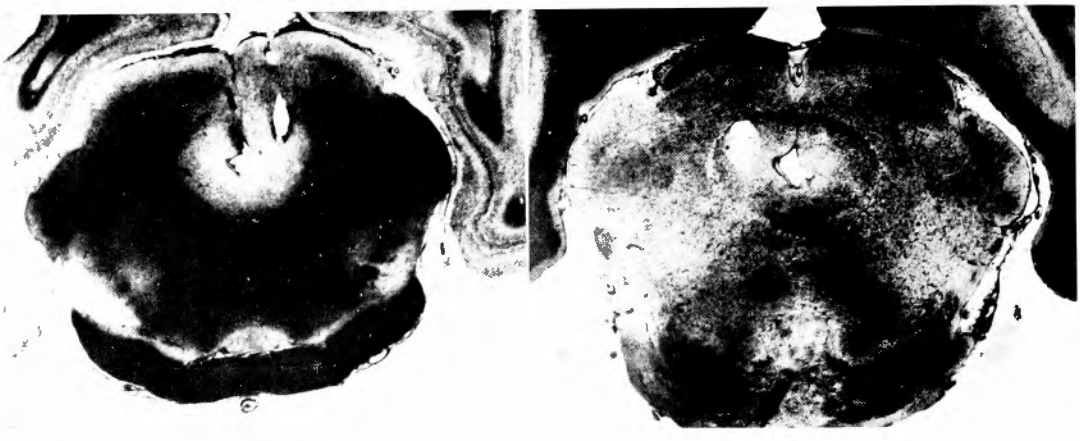
(c) Tonus of muscle

In cases Nos. 11, 19, muscle tonus decreased promptly at the onset of the electrical stimulation and whole body became flaccid, but in cases Nos. 12, 66,

**Fig. 2** Sites of stimulation of 4 cases which fell into coma.
(Transverse section of the midbrain)



No. 11 No. 19



No. 12 No. 66

**Table 5** Conditions of stimulation in 4 coma cases.

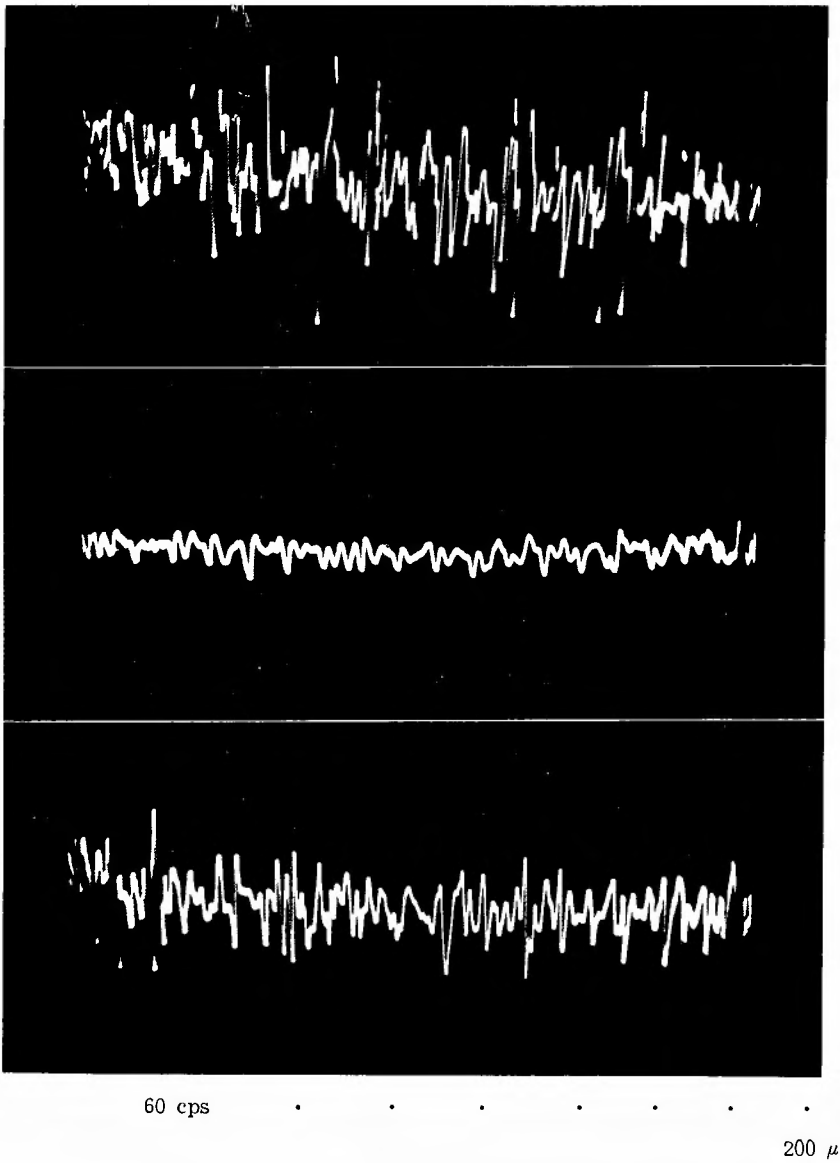
| Case Number | Duration | Voltage | Cycle |
|---|---|---|---|
| No. 11 | 1 msec | 1.5 v | 60 cps |
| No. 12 | 1 msec | 1.5 v | 30～60 cps |
| No. 19 | 1 msec | 1.5～2 v | 60 cps |
| * No. 66 | 1 msec | 1 v | 30 cps |

* The electrode tip was about 2 times larger than in the other 3 cases.

muscle tonus tended somewhat to increase.

In general the stronger the disturbance of consciousness was, the greater the decreasing of muscle tonus was.

**Fig. 3** EMG in a case (No. 11) of coma elicited by square pulse stimulation of the mesencephalic central gray matter.

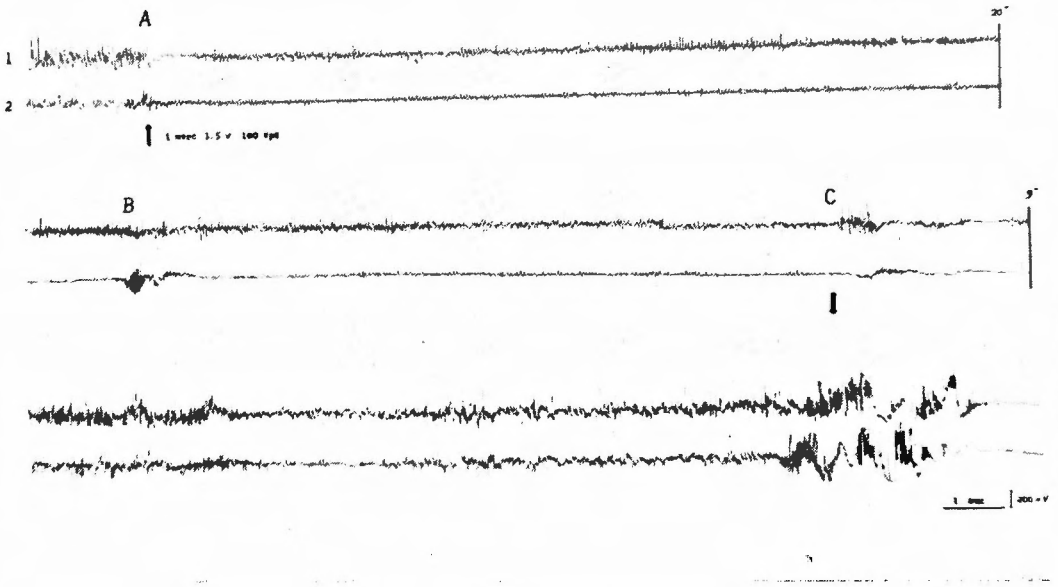



Note:
The EMG was led from r. m. triceps brachii (No. 11).
Bipolar copper electrode ca. 100 μ in diameter, insulated in a syringe needle, was utilized.
Upper records show the interference voltages of shivering or the like.

The EMGs in cases Nos. 11, 19 at the time of coma are shown in Figs. 3 and 4.

As above mentioned, in 4 cases of coma and in cases of semicoma, sham rage reaction etc., stimulated sites were found in the GC But it was not decided which part in the GC was most closely concerned with the disturbance of consciousness.

**Fig. 4** EMG in a case (No. 19) of coma elicited by square pulse stimulation of the mesencephalic central gray matter.




The strip 1 or 2 shows the EMG of contralateral or ipsilateral side (M. biceps femoris) in response to the mesencephalic central gray matter stimulation respectively.

During the period A-C, the square pulse (100 cps, 1.5 volts, 1 msec) was applied in the mesencephalic central gray matter. At the time B, the cat shows a sign of slight movement.

A : Onset of stimulation
A-B : Coma
B-C : Semicoma
C : Cessation of stimulation

Times shown at the right ends of the upper two pairs of records indicate the period of abridgment of the records.

## SUMMARY OF THE RESULTS OF ELECTRICAL STIMULATION

1) Square pulses were used for electrical stimulation. Under the guide of HORSLEY-CLARKE's stereotaxic instrument, mainly the sites near the level of the oculomotor nuclei of the GC of the midbrain in cats were stimulated by monopolar or bipolar electrode (pole distance ca. 0.1 mm or 2 mm) which consisted of steel wire ca. 0.3 mm in diameter insulated with CASHEW's enamel except for ca. 0.3 mm at the tip.

2) The stimulation by monopolar electrode gave rise to no coma. But the stimulation by bipolar electrode with pole distance ca. 0.1 mm, in 1 out of 6 cases, and that with pole distance ca. 2 mm in 4 out of 14 caused temporary coma without accompaning convulsion simultaneously with stimulation.

3) Stimulation conditions in coma cases were 1 msec, 1.5～2 volts, 60 cps. And the significant differences in effects according to the pole distances were not recognized. But only 1 case No. 66 in which the bare tip of the electrode was 2 times

larger than in others, fell into coma at 1 msec, 1 volt, 30 cps i. e. by lower voltage and cycle than in other cases.

4) Concerning the sites of stimulation, the tips of electrodes in all coma cases were located in the GC. However, cases in which electrode was placed in the GC did not always fall into coma, but showed sometimes semicoma and sometimes sham rage reaction. And, stimulated points in 4 out of 5 cases which fell into coma were located in the dorsal part of the GC, and the stimulated point in the remaining 1 was in the ventral part of the GC. But it was not decided which part of the GC was concerned particularly with the consciousness.

5) Concerning the relation between coma and convulsion, the condition of stimulation became stronger, most of the animals developed convulsions and fell into coma simultaneously. But even by the intensity of the stimulation under the threshold of convulsion, coma without accompaning convulsion could be induced though in a few cases.

B) Chemical stimulation

Strychnine, acetylcholine, penicillin, INAH, TEAB were used for chemical stimulation. A little amount of India ink was added to mark the injected sites in histological specimen.

The injection volume was usually about 0.01 cc.

1) Strychnine stimulation

Ca. 0.01 cc of 2%, 1%, 0.25% nitrous strychnine solution respectively was injected in each cat.

Of the 10 cats, 5 revealed to have been injected in the GC, 3 in both the GC and the reticular formation (In the following, reticular formation will be abbreviated as RF), 1 in the RF and the remaining 1 in the SYLVIAN aqueduct histologically.

According to the differences of sites of injection and concentrations of solution, the cats showed various reactions. In general, the cats indicated no loss of noci-reflexes, but on the contrary hyperexcitability, i. e. excessive reaction to touch stimuli. Tonus of muscles also showed the state of exaggeration, and in 3 cases, tonic or clonic convulsion was recognized after the injection.

In cases, which were injected probably in the SYLVIAN aqueduct, convulsion occurred 1~2 minutes after the injection, but in 2 cases which were injected in the GC or in both the GC and RF, it occurred 15~25 minutes later. Respiration was sometimes superficial and accelerated, and active movements were not disturbed.

Among 3 cases, accompanied with convulsion, 1 showed clonic convulsion (C. C.), but retained noci-reflexes during convulsion. But in 2 cases with tonic convulsion (T. C.), coma (noci-areflexia) was induced simultaneously, and the cat died without awaking from coma.

2) Acetylcholine stimulation

20 w/v %, 40 w/v % and 100 w/v % solutions of acetylcholine chloride (Ovisot) were used immediately after being dissolved in distilled water. Injection volume was ca. 0.01 cc.

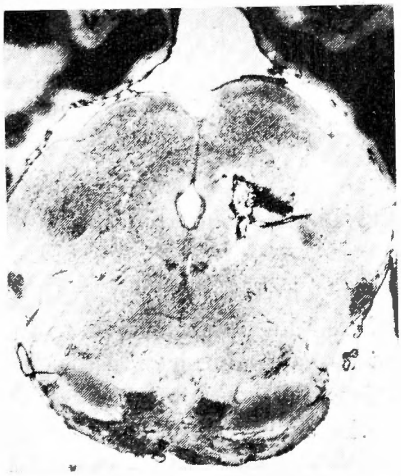
Injection was done in 6 animals. The sites of injection in 2 cases were located

**Table 6** Strychnine stimulation

| Case Number | Sites of Stimulation | Concentration | Convulsion | Disturbance of Consciousness |
|---|---|---|---|---|
| No. 51 | GC | 2% | (−) | (−) |
| No. 27 | GC | 1% | C.C | (±) |
| No. 47 | GC | 1% | (−) | (−) |
| No. 26 | GC | 0.5% | (−) | (−) |
| No. 31 | GC | 0.25% | (−) | (−) |
| No. 28 | GC RF | 2% | (−) | (−) |
| No. 53 | GC RF | 2% | T.C. | Coma |
| No. 29 | GC RF | 1% | (−) | (−) |
| No. 25 | RF | 1% | (−) | (−) |
| No. 50 | SA | 2% | T.C. | Coma |

(Injection volume: ca. 0.01 cc)

**Fig. 5**



No. 51
2% strychnine solution. ca. 0.01 cc. Site of stimulation GC
Coma (−)
Convulsion (−)

Transverse section of the midbrain showing the site of stimulation.

in the GC and in the remaining 4 in both the GC and superior colliculus.

3 out of 6 cases showed lowering of noci-reflexes for a moment immediately after the injection (semicoma I), but the remaining 3 showed "agitation states". Only in 1 case, clonic convulsion occurred suddenly in whole body 20～30 seconds after removing the injection needle, and lasted for 2～3 minutes. This convulsion seemed to be on account of the back flow of acetylcholine solution along the needle track. In other cases there was no convulsion.

Tonus of muscles was accelerated in 1 case, but almost flaccid in the remaining cases, active movements being diminished. Salivary secretion increased in many cases.

Thus, slight disturbance of consciousness (noci-hyporeflexia) can occur from the GC of the midbrain by acetylcholinization, and convulsion seems scarcely to occur.

3) INAH stimulation

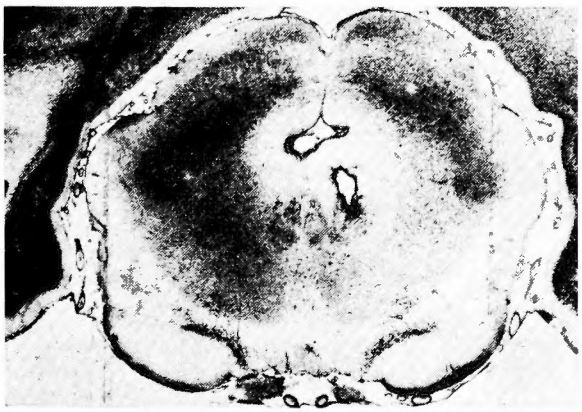
In 3 cases, ca. 0.01 cc of 5 w/v% or 10 w/v% solution respectively of INAH was injected.

**Table 7** Acetylcholine stimulation

| Case Number | Concentration | Sites of Stimulation | Behavior | Convulsion |
|---|---|---|---|---|
| No. 32 | 20 w/v % | GC SC | Semicoma I | (−) |
| No. 33 | 40 w/v % | GC | Excitation | (−) |
| No. 46 | 100 w/v % | GC | Excitation | (−) |
| No. 48 | 100 w/v % | GC SC | Excitation⟶Coma | C. C. after removal of injection needle |
| No. 49 | 100 w/v % | GC SC | Semicoma I | (−) |
| No. 52 | 100 w/v % | GC SC | Semicoma I | (−) |

(Injection volume: ca. 0.01 cc)

**Fig. 6**



No. 46
100 w/v% acetycholine solution. ca. 0.01 cc.
Site of stimulation GC.
Excitation
Convulsion (−)

No. 49
100 w/v% acetylcholine solution. ca. 0.01 cc.
Site of stimulation GC SC.
Semicoma I
Convulsion (−)

Transverse section of the midbrain showing the site of stimulation.

The stimulated portion was rather caudal and in the border area between the GC and the RF or in dorsolateral part of the GC inclusive of the inferior colliculus.

In general, there were few changes in noci-reflexes, and 2 out of 3 cases

developed generalized clonic convulsion about 50 minutes after the injection.

It was particular that the cat cried violently, became excited and showed "sham rage" reaction during convulsion. It seemed that distinct disturbance of consciousness did not occur by INAH, although the injection was done in no cases exactly inside the GC.

**Fig. 7**

INAH stimulation.
No. 37
5 w/v% INAH solution. ca. 0.01 cc.
Site of stimulation GC RF.
Disturbance of consciousness (−)
Convulsion (−)

4) Penicillin stimulation

Crystal penicillin G Na. was used made by BANYU pharmaceutical company. This was dissolved in distilled water so as to contain 500.000, 250.000, 200.000, 100.000, 50.000 or 20.000 i. u. per cc. Solution of each concentration was used in experiment. Injection volume was ca. 0.01 cc. Injection was done in 8 cases. The locations of penicillinization were the GC in 5, both the GC and the RF in 1 and obscure in 2.

By penicillin stimulation, less than 50.000 i. u. per cc in concentration, the animal did not show any marked changes of behavior or convulsion, although more than 100.000 i. u. per cc caused generalized convulsion in all cases.

In 4 of the 6 convulsion cases, distinct clonic seizure occurred in whole body 4～5 minutes after the injection, and the cats fell into coma simultaneously with convulsion and continued the state of coma for 5～15 minutes. But in spite of continuation of convulsion, noci-reflexes were gradually recovered and the cats appeared to have awaked from coma.

In other 2 cases, clonic seizure occurred 15 or 30 minutes after the injection. But it is particular that in these cases, disturbance of consciousness was recognized before the onset of convulsion. Namely, in 1 case, about 30 seconds after the injection, both pupils dilated, and 1 minute later, the reflex to stimuli of nasal tip and septum nasi, and the vomiting reflex to stimuli of pharyngeal mucosa disappeared and the corneal reflex and pinna reflex were sluggish. The active movement and cry

were absent and extremities hung down flaccidly. After the state of coma continued for about 6 minutes, the cat began to cry and showed the agitation state, and about 15 minutes after the injection, the cat developed generalized convulsion. The convulsion was first tonic and next clonic, and the cat fell into coma again for 4～5 minutes, although noci-reflexes gradually recovered in spite of continuation of convulsion. And the cat succumbed 45 minutes after the injection. The site of injection in this case was obscure.

In the remaining 1 case, noci-reflexes decreased immediately after the injection, and the cat fell into semicoma for several minutes. Succeedingly, the twitching appeared in four limbs. The twitching gradually increased its intensity and changed to the generalized clonic convulsion in 30 minutes after the stimulation. During convulsion the cat fell into coma.

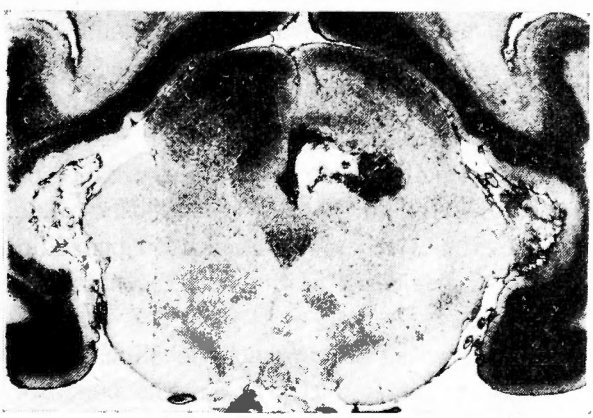
The site of injection in this case was the ventral part of the GC histologically.

**Table 8** Penicillin stimulation

| Case Number | Concentration (per cc) | Sites of Stimulation | Convulsion | Disturbance of Consciousness | |
|---|---|---|---|---|---|
| | | | | Bef. conv. | Dur. conv. |
| No. 39 | 500.000 i. u. | GC | C.C. | (−) | Coma |
| No. 40 | 250.000 i. u. | GC | C.C. | (−) | Coma |
| No. 62 | 200.000 i. u. | GC | C.C. | Semicoma | Coma |
| No. 41 | 100.000 i. u. | obscure | C.C. → T.C. | Coma | Coma |
| No. 42 | 100.000 i. u. | GC | C.C. | (−) | Coma |
| No. 43 | 100.000 i. u. | GC RF | C.C. | (−) | Coma |
| No. 45 | 50.000 i. u. | obscure | (−) | (−) | |
| No. 44 | 20.000 i. u. | GC | (−) | (−) | |

(Injection volume : ca. 0.01 cc)

**Fig. 8**



Penicillin stimulation.
No. 39
500.000 i. u. per cc. ca. 0.01 cc. Site of stimulation GC.
Before convulsion coma (−)
During convulsion coma (+)

5) TEAB stimulation

TEAB solution of 50 w/v % or 100 w/v % was used in this experiment. Injection volume was ca. 0.01 cc. Injection was done in 3 cases. In 2 cases, the site of injection was recognized in the GC and in another it was unknown (probably

in the SYLVIAN aqueduct).

In all 3 cases, disturbance of consciousness was not recognized before the occurrence of convulsion. The latent periods from injection to the occurrence of convulsion were about 15 minutes in GC cases and about 2 minutes in another cases. The convulsion was generalized tonic or clonic, and coma continued during convulsion. One of the animals died 7 minutes after the stimulation without awaking from coma.

**Fig. 9**

No. 59
100 w/v% TEAB solution. ca. 0.01 cc.
Site of stimulation GC.
16 minutes after injection convulsion occurred.
During convulsion coma continued.

## SUMMARY OF THE RESULTS OF CHEMICAL STIMULATION

1) Strychnine, acetylcholine, penicillin, INAH and TEAB which were dissolved in distilled water to a certain concentration were used for chemical stimulation.

2) To mark the sites of injection, a little amount of India ink was added to these solutions. And under the guide of HORSLEY-CLARKE's stereotaxic instrument, the GC of the midbrain was punctured with luetin syringe to inject about 0.01 cc of these solutions.

3) Among these drugs, acetylcholine and penicillin caused some disturbance of consciousness without accompaning convulsion. But disturbance of consciousness due to acetylcholine stimulation was not much distinct, whereas that due to penicillin stimulation was relatively deep. And in case of penicillin stimulation, generalized convulsion occurred in succession to coma in all cases.

4) The convulsion occurred by all these medicines except acetylcholine. In 1 acetylcholine case, convulsion occurred immediately after drawing out the puncture needle, probably due to flow back of acetylcholine solution along the puncture canal.

Most of the cases fell into coma simultaneously with convulsion, but INAH cats showed agitation state during convulsion without loss of noci-reflexes.

Convulsion usually occurred in certain minutes (several minutes—a quarter of one hour) after the injection, but in cases of acetylcholine and penicillin stimulation,

disturbance of consciousness occurred immediately after the injection. This is quite similar to the electrical stimulation. However in electrical stimulation, as soon as the current stops, stimulation effect is lost, while chemical stimulation is effective for a long time, so that disturbance of consciousness associated with convulsion occurring in later stage of chemical stimulation must be discriminated from disturbance of consciousness immediately after injection. What could be compared with coma by electrical stimulation, is the coma immediately after the injection.

## DISCUSSION

According to TODA in our laboratory, in the exeperiments of "coma puncture" by faradic stimulation in the central gray matter of the midbrain in unanesthetized cats, most of the experimental animals indicated temporary stiffness of whole body, restlessness, "sham rage like" agitation with stimulation simultaneously, and fell into coma with final of stimulation and continued coma for about 10 minutes. But in my square pulse stimulation, coma occurred as soon as the current was given, and convulsion did not accompany, and tonus of muscles was flaccid. The coma continued for about 1 minute during stimulation.

Afterward, though stimulation was continued, coma became gradually superficial and the cat arose from coma simultaneously with stop of the current. Namely, the results of my experiment resembled those of electronarcosis by ASAI in our laboratory. ASAI obtained occasionally the state of electronarcosis (coma), when gradually increasing 60 cps alternating current was applied in the ventral part of the mesencephalic central gray matter or in the boundary between it and the reticular formation.

Some of his animals fell into coma suddenly, but most of them became electronarcosis through the agitation phase. Stimulation voltage ranged from 1 to 6.5 volts, and current intensity from ca. 0.01 to 4 mA. But the cases in which stronger stimulation with higher voltage and more current was used to induce electronarcosis, showed more frequently the agitation states (unrestlessness and sham rage) until they fell into coma as compared with the cases which became comatose by lower voltage and less current i. e. weaker stimulation.

HORIGUCHI et al. induced the complete electronarcosis with no apparent convulsive phase by using the tack form electrode made of steel upon the dura of temporal region in rabbit and applying various audiofrequencies of sine wave increasingly. And he stated that it was necessary to increase the stimulation voltage gradually from microdosage first, and to avoid the sharp gradient of voltage in order to reach the state of electronarcosis with no convulsive phase, and if the stimulation dosage was increased abruptly during electronarcosis, tonic or clonic convulsion occurred immediately.

I endeavored to determine the conditions of stimulation for inducing coma with no accompaning convulsion, without using increasing stimulation. In my experiment animals fell into coma without passing through agitation state immediately after relatively weak stimulation. Regardless of the kinds of electrode or methods of

stimulation, there are 2 types of induced coma (unresponsiveness). That is:

1) Animal falls into coma after the end of stimulation and continues disturbance of consciousness as in case of faradic stimulation.

2) Animal falls into coma only for a moment during stimulation and awakes from coma simultaneously with stop of the current as in case of sine wave or square pulse stimulation.

In general, before the onset of coma, stiffness of whole body, restlessness, "sham-rage-like" agitation are to be seen in the former type, but are few in the latter, at least in my experiment. In the latter the cats fall into coma almost simultaneously with stimulation, but coma continues only for a moment in the course of stimulation and not for a long time. To induce long lasting disturbance of consciousness in animals, strong stimulation is necessary, which however is liable to be accompanied with secondary reaction i. e. generalized stiffness, unrestlessness, "sham-rage-like" reaction and sometimes generalized convulsion. It seems difficult to induce coma which persists after the termination of stimulation by using weak stimulation avoiding secondary reactions.

By faradic currents the explosive abnormal stimulation of the midbrain tends to be effected, thus causing occasionally coma persisting after the termination of stimulation, although the coma is liable to be preceded by convulsions.

On the other hand, by weak square pulse, it is difficult to obtain strong stimulation momentarily and to induce convulsion. But if the stimulation is exerted under a certain condition, it may disturb the function of the stimulated region so as to cause coma. From the fact that during current flow noci-reflexes are gradually recovered it may be assumed that the animal is gradually accustumed to the stimulation.

Asai used for electronarcosis gradually increasing sine wave. In this way stimulation by voltage gradient can be avoided, so that coma can be obtained by the stimulation at relatively high voltage without apparent initial convulsion. For the same reason the relatively wide ranges of stimulation conditions in his experiment, such as 1～6.5 volts, ca. 0.01～4 mA may be explained.

In my experiments of square pulse stimulation by monopolar or bipolar electrode, the cases which fell into coma without accompaning convulsion were only 5 out of all 26 which were stimulated in the GC of the midbrain, and moreover, all these 5 cases were stimulated by bipolar electrode at about 1 msec, 60 cps, 1.5～2 volts.

The cats, in which the tip or tips of electrode were located in the GC of the midbrain histologically, did not always fall into coma, but more frequently showed "sham rage" or agitation states. However, the fact that the cases which were stimulated in the parts other than the GC did not fall into coma, is considered to indicate the particular importance of the GC of the midbrain for the maintenance of consciousness.

In chemical stimulation, Yabuno in our laboratory, made an experiment of nicotinization in the brain stem in unanesthetized cats. By nicotine injection in the central gray matter at the level between the oculomotor and the trochlear nuclei

inclusively, the cat tended to fall into coma without accompaning convulsion, and the coma persisted for a relatively long time (15～40 minutes).

In 5 sorts of chemical stimulation of the present experiment, however, disturbance of consciousness without accompaning convulsion was recognized only by acetylcholine and penicillin stimulation. Moreover, disturbance of consciousness by acetylcholine was slight, showing "semicoma I" for a moment. By penicillin some fell into coma or semicoma without accompaning convulsion immediately after the injection, but all of them developed generalized convulsion at a certain time after injection (several minutes — a quarter of one hour). In other chemical stimulations, there were no cases of disturbance of consciousness without accompaning convulsion, though nearly all animals fell into coma simultaneously with generalized convulsion, which occurred in many cases after a fairly long time such as several minutes to about a quarter of one hour after the injection, the time probably depending upon the concentration of the injected medicines. It is assumed that the action of the injected chemicals continues for some time after injection. In this regard it differs electrical stimulation. But in considering the disturbance of consciousness in relation to commotio cerebri the coma immediately after the injection analogous with that due to the electrical stimulation may be more important than the coma following convulsion which occurs in later stage.

Moreover, in convulsion by INAH, the cats did not fall into coma, but showed the agitation states.

In chemical stimulation, it is very difficult to determine the adequate conditions to cause coma. It is my impression that the coma in this case is closely connected with convulsion, and scarcely occurs without accompaning convulsion.

## SUMMARY

Experiment has been made to induce coma by electrical (24 cases) or chemical (30 cases) stimulation at the level of the oculomotor nuclei in the central gray matter or the neiboring structures of the midbrain in unanesthetized cats.

1) By square pulse stimulation in 24 cases (sites of stimulation 26), temporary coma without accompaning convulsion occurred simultaneously with the onset of stimulation in 5 cases, in which stimulation was done in the central gray matter of the midbrain.

2) In 20 cases (sites of stimulation 23) of electrical stimulation by bipolar electrode, temporary coma without accompaning convulsion was obtained in 5 cases and the stimulation conditions in these 5 cases were about 60 cps, 1.5～2 volts, 1 msec regardless of pole distance of the bipolar electrode.

3) Coma was induced for some time (about 1 minute) in the course of electrical stimulation. But the cats awaked simultaneously with stop of electrical stimulation.

4) For chemical stimulation, strychnine was injected in 10 cases, acetylcholine in 6, INAH in 3, penicillin in 8 and TEAB in 3.

5) Only in 2 cases of penicillin injection, coma or semicoma was induced

without accompaning convulsion. But after awaking from unconsciousness, generalized convulsion occurred.

Slight disturbance of consciousness was obtained also by acetylcholine injection.

ABBREVIATIONS IN TABLES AND FIGURES

| | |
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| GC | Central gray matter of the midbrain |
| RF | Reticular formation of the midbrain |
| SA | SYLVIAN aqueduct |
| SC | Superior colliculus |
| C.C. | Clonic convulsion |
| T.C. | Tonic convulsion |
| Bef. conv. | Before convusion |
| Dur. conv. | During convulsion |

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## 和文抄録

# 中脳中心灰白質の電気刺戟及び化学刺戟によつて痙攣を伴わない昏睡を来す可能性

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動物に於て昏睡（無反応状態）を誘起する場合に，屢々昏睡と同時に痙攣を伴う事があるが，これは痙攣による二次的な意識障害と紛わしい．本研究では猫の中脳中心灰白質（主として動眼神経核附近）を電気及び化学物質により刺戟した時に痙攣を伴わない昏睡を誘起出来る可能性について実験を行つた．

(1) 電気刺戟

矩形波により単極或いは双極(極間距離，約0.1mm及び2mm)電極を用いて漸増する事なく一定の条件にて刺戟を行うに，24例中（刺戟点26）5例に痙攣を伴わない一過性の昏睡を誘起出来た．

痙攣を伴わない昏睡はすべて双極刺戟の場合で，自家製の電極では刺戟条件は30～60 cps, 1.5～2 volts, 1 msecの略々一致した値が得られた．昏睡は刺戟直後より通電中の短時間(約1分間)のみ持続し，その後は通電中にも拘らず次第に意識障害の程度は浅くなり，通電を遮断すれば昏睡より直ちに覚醒する．

(2) 化学刺戟

Strychnine, Acetylcholine, INAH, Penicillin, TEABの5種の薬物を夫々蒸溜水に溶解して適当な濃度とし，約0.01cc注入したが，注入直後痙攣を伴わない昏睡に陥つたのは Penicillin 刺戟による1例のみであり，而も後期になつて痙攣が発現した．

薬物による刺戟では多くの場合注入後数分乃至十数分という相当長時間後に痙攣が起り同時に昏睡に陥るが，我々が脳振盪との関聯に於て重視したいのは注入直後の昏睡であり，後期になつて起る痙攣とそれに伴う意識障害とは区別して考えたい．

以上，電気刺戟に於ても，昏睡と痙攣とは表裏一体というか，紙一重の密接な関係にあるので，痙攣を伴わない昏睡を得る事は非常に困難であるが，非常に狭い範囲の至適条件によつて痙攣を伴わない昏睡を誘起することが可能である．